

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of KOGAMI Kenji, et al.

Appln. No. 10/523,287

Group Art Unit: 1626

Filed: February 3, 2005

Examiner: Robert Havlin

For: PROCESS FOR PRODUCING N-MONOALKYL-3-HYDROXY-3-(2-THIENYL)PROPANAMINE AND INTERMEDIATE

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

I, SATAKE Syuzo, hereby declare:

- 1) That I am one of the inventors of the instant invention:
- 2) That the experiments given below were carried out under my general direction and supervision.

Experimental Example 1

Preparation of (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine
88.1 g (0.50 mol) of the sodium salt of β -oxo- β -(2-thienyl)propanal and 168 g of methanol were introduced into a 1-liter 4-necked flask equipped with a stirrer, condenser, thermometer and dropping funnel. 87.8 g (0.50 mol) of a 38.5 wt.% aqueous monomethylamine hydrochloride solution was added dropwise at 25°C over 20 minutes. After the dropwise addition, reaction was carried out at 30°C for 5 hours.

After the reaction, methanol was distilled off, and 121.4 g of a 3.1 wt.% aqueous sodium hydroxide solution and 300 g of methyl *t*-butyl ether were added for phase separation. The organic layer obtained by the separation was kept at 40°C and the solvent was distilled off, the thus-precipitated crystals were then filtered. The crystals thus obtained were washed twice with 100 g of ethanol and dried, thereby giving 62.5 g

(0.374 mol) of (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine. The yield thereof based on the sodium salt of β -oxo- β -(2-thienyl)propanal was 74.8%.

Analysis of (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine

- (1) Solid NMR¹³C-nuclear magnetic resonance spectrum (TMS standard) δ (ppm): 39.11, 91.08, 129.70, 132.25, 134.21, 149.51, 158.53, 184.80
- (2) Melting point (DSC measurement): 85.3 to 86.4°C

Experimental Example 2

Preparation of (E)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine

83.6 g (0.50 mol) of (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine obtained in the same manner as in Experimental Example 1 and 332.2 g of methyl t-butyl ether were introduced into a 1-liter 4-necked flask equipped with a stirrer, condenser, thermometer and dropping funnel, followed by crystallization while stirring at 25°C for 5 hours.

After subjecting the deposited crystals to filtration, the crystals thus obtained were washed twice with 100 g of methyl t-butyl ether and dried, giving 70.2 g (0.42 mol) of (E,Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine. By conducting separation using a sieve having openings of 100 μ m, 3.5 g (0.02 mol) of (E)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine was obtained. The yield of (E)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine was 4.2% based on the (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine used.

Analysis of (E)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine

- (1) Solid NMR¹³C-nuclear magnetic resonance spectrum (TMS standard) δ (ppm): 30.09, 91.08, 129.70, 132.25, 134.21, 149.51, 158.73, 184.80
- (2) Melting point (DSC measurement): 65 to 66°C

Difference between (Z) isomer and (E) isomer

According to the solid NMR measurement results, Z isomer differs from E isomer in that Z isomer showed a signal at 39.11 ppm and E isomer showed a signal at 30.09 ppm. It is

assumed that these signals correspond to the signals of carbon atoms of the CH₃ group adjacent to the amino group, and such difference is attributable to the difference in the geometrical isomerism between *Z* isomer and *E* isomer.

Results of melting point measurements indicate that *Z* isomer has a melting point that is about 20°C higher than that of *E* isomer. This makes *Z* isomer more advantageous than *E* isomer in industrial use, because, for example, crystals of *Z* isomer do not easily solidify in a drying step.

I, the undersigned, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 2008. 10. 22

Satake Syuzo
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